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<p>(54) Title: COMPOSITION FOR IRRIGATING INTRAOCULAR TISSUES AND MAINTAINING MYDRIASIS DURING INTRAOCULAR SURGERY</p> <p>(57) Abstract</p> <p>An improved pharmaceutical composition useful in ophthalmic surgery is described. The composition includes a mydriatic agent, such as epinephrine in an acidic solution. The acidic solution preferably also contains glutathione. The composition is preferably formulated as a two-part solution, with the mydriatic agent being included in a relatively small volume, acid solution, and one or more electrolytes being included in a neutral, buffered solution having a relatively large volume.</p>		

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**COMPOSITION FOR IRRIGATING INTRAOCULAR TISSUES
AND
MAINTAINING MYDRIASIS DURING INTRAOCULAR SURGERY**

Cross Reference to Related Application(s):

The present application is a continuation-in-part of United States Patent Application Serial No. 07/964,327 filed October 21, 1992.

Background of Invention:

5 1. Field of the Invention

The present invention relates to the field of intraocular surgery. More particularly, the invention relates to a solution which performs the dual functions of: (1) maintaining mydriasis, and (2) maintaining the integrity, stability, and function of ocular tissues, during invasive intraocular surgical procedures.

10 2. Discussion of Related Art

The growth of new surgical techniques and associated products over the past decade has been quite remarkable. For example, cataract surgery, which is a very delicate operation involving replacement of the natural crystallin lens of the human eye with an artificial lens, was previously considered to be a major surgical procedure requiring hospitalization of the patient and a significant recovery period, but today this procedure is routinely performed on an out-patient basis and enables vision to be restored almost immediately. Similar advancements have been achieved in other areas of ophthalmic surgery. These remarkable advancements are attributable to various factors, including improved equipment for performing the surgeries, improved surgical techniques developed by innovative surgeons, and improved pharmaceutical products which facilitate successful surgery by minimizing the risks of damaging sensitive, irreplaceable ocular tissue during surgery. The present invention is directed to a further improvement in one such

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pharmaceutical product, a solution for irrigating ocular tissue during intraocular surgery. Such solutions are discussed in United States Patent No. 4,550,022; the entire contents of that patent are hereby incorporated in the present specification by reference. The importance of such solutions to ophthalmic medicine is explained in the '022 patent. The relevant portions of that explanation are repeated below.

Any scission into the human body is detrimental to the human body and invariably results in cell loss. The need to keep cell loss to a minimum is particularly crucial during any surgical procedure performed on delicate and irreplaceable tissues, such as the tissues of the eye, nerves, etc.

The cornea of the eye is comprised of five layers: epithelium, Bowman's membrane, stroma, Decemet's membrane, and endothelium. The endothelium layer is particularly vulnerable to trauma as the endothelial cells are infrequently, if ever, replaced as a normal process in the adult life. The endothelium is principally responsible for the maintenance of the proper state of hydration of the stromal layer. The stromal layer has a tendency to imbibe fluid, a tendency which is counter-balanced by outward fluid transport via the endothelium. If the proper fluid balance is not maintained in the stromal layer, the cornea thickens and the characteristic transparency of the cornea is lost. Accordingly, cell loss or damage in the endothelial layer will result in decreased vision. Failure of the endothelium to perform its fluid transport function for short periods of time will result in corneal thickening and visual clouding. Because of the importance of, and the vulnerability of, the endothelial layer, it is necessary during eye surgery, such as cataract and retinal surgery or corneal transplants, to make provisions for the protection of the endothelial cells.

A significant factor causing cell loss during tissue scission is the traumatic change in environment experienced by the internal cells. Exposure to the atmosphere presents a far different environment for the cells than is provided by the natural fluids in which they are bathed. To simulate the natural cellular environment and thereby prevent cell damage, exposed tissue during surgery is frequently irrigated in solutions which attempt to approximate natural body fluids. The value of bathing eye tissue during surgery to prevent cell damage has long been recognized. For internal ocular tissues, such as the endothelium, the aqueous humor is the natural bathing fluid and, hence, an ophthalmic irrigating solution intended to protect the endothelium should as closely as possible resemble the aqueous humor.

Of primary concern in a tissue irrigating solution is that the osmolality of the solution be generally isotonic with cellular fluids so as to maintain equal osmotic pressure within and without the cell membranes. To this end, one of the early ophthalmic irrigating solutions was isotonic (0.9%) saline. However, as has long been recognized, isotonic saline is quite inadequate as an ophthalmic irrigating solution and has been shown to result in endothelial cell swelling, cell damage, and consequent corneal clouding.

Because of the inadequacy of isotonic saline, various alternative electrolyte solutions have been proposed as ophthalmic irrigating solutions in attempts to provide solutions which more closely resemble the aqueous humor and prevent cell damage and corneal clouding. Standard electrolyte solutions primarily intended for injection solutions, such as Ringer's solution and lactated Ringer's solution, have been used as ophthalmic irrigating solutions because of their wide availability as sterile solutions.

A solution intended for ophthalmic irrigation known as "balanced salt solution" has also been developed. Balanced salt solution contains the essential ions, calcium, sodium, potassium, magnesium and chloride in generally optimal concentrations for ocular tissue, and has an acetate-citrate buffer system which is compatible with divalent calcium and magnesium ions.

The various electrolyte solutions used for ophthalmic irrigation have been improvements over normal saline by providing necessary ions in addition to Na^+ and Cl^- as provided by isotonic saline. Mg^{++} is an important cofactor for adenosine triphosphatase, an enzyme which plays an important role in mediating the fluid transport pump in the eye. Ca^{++} is necessary to maintain the endothelial junction. K^+ is an important factor in many biochemical processes, and the fluid transport pump of the endothelium requires a proper Na^+/K^+ ratio.

During eye surgery and particularly during surgery which requires extended periods of time, proper electrolytic balance alone is insufficient to retain normal corneal thickness. To maintain proper corneal thickness and prevent cell damage, an irrigating solution in addition to electrolytic balance must provide metabolic support and must particularly provide factors needed for the enzyme-mediated Na^+/K^+ pump system through which excess fluid is removed from the stroma.

To incorporate factors necessary for sustained metabolism by endothelial cells, glutathione-bicarbonate-Ringers solution ("GBR") was developed in which NaHCO_3 ,

glutathione, dextrose and adenosine (an optional ingredient) are added to Ringer's solution. Bicarbonate, dextrose and glutathione have been shown to be important factors in maintaining structural integrity of endothelial cells. Bicarbonate is included because the aqueous humor has a bicarbonate buffer system; dextrose (d-glucose) provides a substrate for various metabolic pathways; and glutathione has been shown to aid the metabolic pump mechanism by maintaining proper Na^+/K^+ adenosine-triphosphatase. GBR has been shown effective in maintaining corneal thickness and endothelial cell integrity for up to three hours.

While the effectiveness of a GBR ocular irrigating solution has been known for many years, prior to the early 1980's its use in surgery was quite limited due to stability and sterility problems. It is to be appreciated that sterility of an ophthalmic irrigating solution is absolutely essential. To insure sterility, it is desirable that an irrigating solution be prepackaged so that the quality and sterility may be closely monitored and tested as contrasted with an extemporaneously mixed solution as might be prepared in a hospital pharmacy. The solution will perfuse the eye in essentially a closed system where even a small number of organisms, such as *pseudomonas aeruginosa*, can produce an overwhelming endophthalmitis. GBR may not be prepackaged due to the long term incompatibility and/or instability of its various moieties. Of the moieties added to Ringer's solution to formulate GBR, bicarbonate is perhaps the most important. The bicarbonate as well as the phosphate in a bicarbonate-phosphate buffer system may form insoluble precipitates with Mg^{++} and Ca^{++} . While at the ionic concentrations useful in ophthalmic irrigation, precipitation is not a problem in freshly prepared solution, long-term storage is proscribed. As insoluble crystals introduced into the eye will cloud vision, the importance of keeping a tissue irrigating solution free of insoluble precipitates may be readily appreciated.

Complicating the maintenance of GBR's stability is the fact that the pH of GBR will gradually increase due to the inadequacy of the bicarbonate-phosphate buffer. To provide proper pH, i.e., about 7.4, the pH of the original GBR solutions prepared in the hospital pharmacy had to be monitored and adjusted with CO_2 immediately prior to use and even during use. The chances for contamination during pH adjustment was great.

A further factor which proscribes long-term storage of GBR is the unavailability of a proper pH at which all of the moieties are stable. Several moieties of GBR are unstable at the physiological pH of about 7.4. Below a pH of about 8, bicarbonate generally decomposes to CO_2 , resulting both in a loss of bicarbonate concentration and increased pH.

On the other hand, glucose stability requires a pH of less than about 6. Glutathione, while biologically effective either in reduced or oxidized form, is preferred in the oxidized form because the reduced form quickly oxidizes in aqueous solutions, preventing proper labeling of the irrigating solution. Oxidized glutathione (glutathione disulfide) is unstable over extended periods of time at a pH of above about 5. The concentration of glutathione may also decrease to an unacceptable concentration when stored over long periods of time in admixture with all other components. Because of the demonstrated efficacy of GBR as an ocular irrigating solution, it was highly desirable to provide a formulation which contains the essential factors found in GBR and which could be stored in a sterilized form for use in eye surgery. The invention described in U.S. Patent No. 4,550,022 provided such a product.

An embodiment of the two-part irrigating solution described in U. S. Patent No. 4,550,022 known as "BSS Plus® Intraocular Irrigating Solution" was introduced by Alcon Laboratories, Inc. in the early 1980's. Although that product has been remarkably successful in both a scientific and commercial sense, the need for inclusion of adjunctive drugs has become increasingly apparent. More specifically, it has been noted that ophthalmic surgeons are in many cases adding adjunctive drugs to BSS Plus® following mixing of the two parts of the product. While this sort of practice is not uncommon (i.e., physicians frequently add drugs to intravenous solutions), it does present added risks with respect to possible inappropriate final drug concentrations, and chemical or microbial contamination of the solution, and is generally not convenient for the physician or operating room personnel. It is, therefore, highly desirable to include adjunctive drugs directly in the irrigating solution at the time of manufacture, if possible. Unfortunately, as discussed above, these solutions tend to be complex in terms of chemical incompatibilities, required pH conditions, and so forth. This is also true of many of the adjunctive drugs which ophthalmic surgeons may desire to add to the solution. One such drug is epinephrine.

Epinephrine is frequently used in the field of ophthalmology to effect dilation of the pupil (i.e., mydriasis). The use of this drug is particularly prevalent in ophthalmic surgical procedures, since dilation of the pupil is frequently necessary in order to increase surgeons' ability to see inside the eye with the aid of a microscope. More specifically, dilation of the pupil during intraocular surgery is necessary to allow visualization and manipulation of tissues which lie behind the plane of the iris, including the lens, retina, and all ocular

structures in the posterior segment. Pupillary dilation is accomplished by the use of sympathomimetic agents which stimulate the iris dilator muscle.

Intraocular injections of epinephrine are frequently used during ophthalmic surgical procedures to produce and maintain mydriasis during surgery. The epinephrine may be injected directly in the eye and/or may be administered as an added component of a surgical irrigating solution. The epinephrine added to intraocular irrigating solutions for constant infusion into the eye during the surgical procedure commonly consists of commercial products intended for parenteral administration. Parenteral preparations, however, may contain undesirable additives such as sodium bisulfite, an antioxidant, and chlorobutanol, a preservative. The pH, osmolality, and buffer capacity of parenteral epinephrine preparations may also be inappropriate for intraocular use. Prior studies have shown that the intraocular use of parenteral epinephrine formulations can cause corneal swelling and loss of corneal endothelial cells. See Edelhauser, et al., "Corneal Edema and the Intraocular Use of Epinephrine", American Journal of Ophthalmology, volume 93, pages 327-333 (1982).

The pH, osmolality and buffering capacity of solutions injected into the eye are critical. The eye contains a relatively small volume of fluid (i.e., aqueous humor), and much of this fluid is lost as a result of the intraocular surgery. Consequently, there is very little natural fluid remaining in the eye to dilute the deleterious effects of a foreign solution which has a pH, osmolality and/or buffering capacity which is incompatible with intraocular tissues. For these reasons, the introduction of even a very small volume of a physiologically incompatible solution into the eye can have a very serious effect on the viability and function of extremely delicate intraocular tissues, such as the corneal endothelium. In contrast, the injection of fluids into the blood stream involves the introduction of volumes which are quite small in relation to the volumes of the receiving medium (i.e., the blood). Moreover, in the case of intramuscular injections, the tissues at the site of the injection are not nearly as sensitive to shifts in chemical equilibrium nor as critical to normal physiological functions as intraocular tissues. The criteria for formulating and utilizing parenteral preparations are therefore fundamentally different from the criteria for formulating and utilizing intraocular solutions.

Recently a preservative-free, sulfite-free sterile epinephrine solution was developed for cardiovascular use in children and asthmatics and has been purchased by ophthalmologists for use as an intraocular irrigating solution additive. This sterile

preparation allows the administration of epinephrine intraocularly without the associated toxic effects of preservatives. See Slack, et al., "A Bisulfite-free Intraocular Epinephrine Solution", American Journal of Ophthalmology, volume 110, pages 77-82 (1990). However, even this sterile, non-preserved epinephrine solution bears risks associated with extemporaneous compounding, such as concentration errors and contamination of the solution during preparation.

The administration of an improper concentration of a sympathomimetic agent during intraocular surgical procedures can have serious consequences. The administration of a low concentration (i.e., relative to the desired concentration) is generally not a problem, since the surgeon will recognize that mydriasis is not being maintained and will therefore supplement the initial administration of the sympathomimetic agent. However, the administration of a high concentration is potentially dangerous. Sympathomimetic agents such as epinephrine constrict blood vessels and thereby restrict blood flow. This restricted blood flow may conceal the need to cauterize a blood vessel during a surgical procedure. After the surgery is completed and the vasoconstrictive effect of the sympathomimetic agent has subsided, intraocular bleeding will occur. This condition, known as hyphemia, will cause the eye to look very bloodshot, and may require surgical intervention in order to stop the bleeding.

Epinephrine is known to be chemically unstable because it is very susceptible to oxidation when in solution. Since intraocular irrigating solutions, particularly GBR solutions such as BSS Plus® Intraocular Irrigating Solution are already complex in terms of the number of components, the chemical incompatibility of certain components, and particular pH conditions needed to maintain the stability of some components, the addition of an another component known to be relatively unstable in solution presents a significant problem.

In view of the foregoing problems, there is a need for an improved intraocular irrigating product which contains a sympathomimetic agent to maintain mydriasis during intraocular surgical procedures.

Summary of the Invention:

A principal objective of the present invention is the provision of a standardized ophthalmic pharmaceutical composition for maintaining mydriasis and irrigating intraocular tissues during intraocular surgical procedures. As utilized herein, the term "standardized" denotes a composition which has certain specified characteristics and properties, and which

is substantially ready for use by ophthalmic surgeons at the time of surgery, without requiring any further, concentration calculations, dilutions, pH adjustments, or other activities generally associated with the preparation of pharmaceutical compositions:

As discussed above, the extemporaneous addition of parenteral epinephrine preparations to ophthalmic irrigating solutions at the time of surgery presents several significant risks, such as the risk of an improper concentration of epinephrine being utilized. The present invention eliminates these risks by providing an ophthalmic pharmaceutical composition containing epinephrine or a similar mydriatic agent which is specifically formulated and adapted for use as an intraocular irrigant. Specific advantages of the compositions of the present invention therefore include: (1) delivery of a specified, controlled dose of a mydriatic agent to the patient, (2) assurance that the composition is sterile at the time of use, (3) elimination of chemical preservatives, such as sulfites, and other ingredients of parenteral preparations which are potentially damaging to intraocular tissues, and (4) adaptation of the pH, osmolality and buffering capacity of the composition so that it is ideally suited for intraocular use. These advantages and other features of the present invention are discussed in greater detail below.

The intraocular irrigating compositions of the present invention includes a first part containing a mydriatic agent. The first part is formulated as an acidic solution. This solution may be lyophilized to form a powder which is then resolubilized prior to administration to the eye. The low pH of the solution improves the stability of the epinephrine. The first part preferably also includes glutathione.

The intraocular irrigating compositions of the present invention also include a second part containing a buffer to provide an ophthalmically acceptable pH when the first and second parts are combined. The first part preferably also includes one or more electrolytes to facilitate the maintenance of normal cellular function during intraocular surgical procedures. Combining the first part and the second part provides a physiologically balanced, standardized solution for maintaining mydriasis while maintaining the function and integrity of intraocular tissues.

Description of Preferred Embodiments:

The irrigating compositions of the present invention contain one or more agents to produce and maintain mydriasis during an intraocular surgical procedure. Such agents are

referred to herein as "mydriatic agents". The mydriatic agents used in the present invention are catecholamines having sympathomimetic activity. As utilized herein, the term catecholamine denotes compounds which include a catechol group (O-dihydroxybenzene) and an amino group on the side chain. The preferred compounds include epinephrine; phenylephrine; dipivalyl epinephrine; norepinephrine; isoproterenol; and the pivaloyloxy and phenylacetyloxy ester derivatives of epinephrine and norepinephrine described in U.S. Patents Nos. 3,809,714; 3,839,584; and 4,085,270. The entire contents of those patents are hereby incorporated in the present specification by reference. Epinephrine and dipivalyl epinephrine ("DPE") are particularly preferred. The l-isomer of epinephrine is approximately 20 times more active than the d-isomer; use of the l-isomer is therefore preferred. The irrigating solutions of the present invention will typically contain one or more mydriatic agents in an amount of about 0.0005 to 0.11 mM/l.

The irrigating solutions of the present invention are formed by combining two or more parts immediately prior to an ophthalmic surgical procedure. The above-described mydriatic agents are contained in a first part which is formulated as an acidic composition. These agents, particularly epinephrine, are relatively stable in an acidic environment. A pH of from about 3 to about 5 is preferred. A pH of about 3 is most preferred for epinephrine. The acidity of the solutions greatly enhances the stability of the mydriatic agents, particularly epinephrine.

The acidic compositions containing one or more mydriatic agents preferably also contain glutathione to assist in the maintenance of corneal endothelial cells. As used herein, "glutathione" encompasses both the reduced (i.e., sulfhydryl) and oxidized (i.e., disulfide) forms of this compound; however, use of the oxidized form of glutathione is preferred. Glutathione is available from various commercial sources.

The invention may be embodied in various types of irrigating solutions. The most preferred embodiment is a two-part product similar to BSS Plus® Intraocular Irrigating Solution (Alcon Laboratories, Inc., Fort Worth, Texas USA). The first part is an acidic solution containing one or more mydriatic agents, and preferably also glutathione. The second part is a buffered, neutral solution containing one or more electrolytes. The compositions of the two parts are such that each is individually stable and may be separately stored for long periods. When the first and second parts are combined, the resulting solution is useful for ocular surgery as it contains the necessary factors to maintain mydriasis, as well

as maintain endothelial cell integrity and corneal thickness, during an intraocular surgical procedure. More specifically, when the first and second parts are combined, the resulting irrigating solution contains: one or more mydriatic agents to maintain mydriasis during the procedure; electrolytes necessary for tissue stability, Ca^{++} , Mg^{++} , Na^+ , K^+ and Cl^- , in a bicarbonate-phosphate buffer; glutathione; and dextrose. The electrolytes are provided in proportions conducive to maintaining the physical integrity and metabolism of corneal endothelial cells and other ocular tissues. For this purpose, the irrigating solution formed by combining the above-described first and second parts will typically contain from about 50 to about 500 millimoles per liter ("mM/l") Na^+ , from about 1 to about 10 mM/l K^+ , from about 0.1 to about 5 mM/l Ca^{++} , from about 0.1 to about 10 mM/l Mg^{++} and from about 50 to about 500 mM/l Cl^- . To maintain the osmotic stability of the cells, the osmolality is between about 260 and about 330 mOsm and preferably about 290-310 mOsm. So as to closely match the physiological pH of 7.4, the pH of the final irrigating solution is between about 6.8 and about 8.0 and preferably about 7.2-7.8. To maintain the fluid pump system, the bicarbonate concentration in the combined irrigating solution is between about 10 and about 50 mM/l. To stabilize the pH, an additional buffering agent is provided. Preferably the buffering agent is phosphate which is provided in sufficient quantity so that final phosphate concentration of the irrigating solution is between about 0.1 and about 5 mM/l. The final irrigating solution contains between about 1 and about 25 mM/l glucose and between 0.01 and about 3 mM/l of glutathione.

The neutral, buffered solution provides the phosphate and bicarbonate buffering moieties, preferably in the form of dibasic sodium phosphate and sodium bicarbonate. The pH of the solution is adjusted to about the physiological pH, of 7.4, preferably to between about 7.2 and about 7.8. As hereinbefore mentioned, the pH of a bicarbonate-containing solution is preferably above about 8.0 to prevent decomposition of the bicarbonate. However, the bicarbonate may be stabilized if it is added to a solution with a pH of above about 8 and thereafter adjusted to a pH between 7 and 8. Accordingly, when the neutral, buffered solution is prepared, Na_2HPO_4 is added prior to the addition of NaHCO_3 so that NaHCO_3 is dissolved in a solution with a pH of between about 8 and 9. The solution is thereafter adjusted with dilute acid, such as H_2SO_4 , H_3PO_4 or HCl , to the desired final pH of the neutral, buffered solution. Alternatively, carbon dioxide may be added to adjust the pH.

Potassium and additional sodium are provided in the neutral, buffered solution in the form of sodium and potassium salts, such as sodium or potassium chlorides, sulfates, acetates, citrates, lactates, and gluconates. The sodium and potassium are compatible with all of the moieties present in the finished tissue irrigating solution, and sodium chloride and potassium chloride may be added to either solution or divided between the solutions. However, in view of the fact that the neutral, buffered solution provides the buffer system, the pH of the final irrigation solution may be more accurately determined if all compatible salts are included in that solution.

In addition to one or more mydriatic agents, the acidic solution preferably also includes Ca^{++} in the form of calcium chloride, Mg^{++} in the form of magnesium chloride, glutathione and dextrose. The pH is adjusted to below about 5 to provide long-term stability to the mydriatic agent, glutathione and dextrose. When epinephrine is utilized as the mydriatic agent, a pH of 3 is most preferred for the acidic solution, since this pH has been found to be optimal for enhancing the stability of epinephrine.

As indicated above, the compositions of the present invention are standardized. More specifically, the volumes of the neutral, buffered solution and the acid composition are selected so that adding the entire acid composition to the entire neutral, buffered solution results in a solution which contains an amount of one or more mydriatic agents effective to maintain mydriasis during an intraocular surgical procedure, and has a pH, osmolality and buffering capacity adapted for irrigation of intraocular tissue. This eliminates the need to calculate concentrations, measure volumes and/or perform dilutions, all of which create risks of concentration errors and microbial contamination. Because of the requirement that the acidic solution have a low pH, it is preferable that the volume of the neutral, buffered solution greatly exceed the volume of the acidic solution and that the acidic solution contain no buffering agents. The acidic solution may be adjusted below a pH of about 5 with a relatively small amount of HCl. Because the acidic solution is unbuffered, its pH is a reflection of the acid concentration and less acid is needed to adjust the pH of a small volume. The large volume of neutral, buffered solution may be adjusted very close to the final pH of the irrigating solution and will be relatively unaffected by the addition of the small volume of the acidic solution. Preferably, the ratio of the volume of the neutral, buffered solution volume to the acidic solution volume is about 10 to 1 to about 50 to 1. A ratio of 25 to 1 is particularly preferred.

If the acidic composition is provided in the form of a solution, rather than a lyophilized powder, the use of a relatively concentrated, small volume solution is preferred. The use of a more concentrated solution is believed to enhance the stability of mydriatic agents such as epinephrine when those agents are in solution. In the absence of an antioxidant, epinephrine breaks down through two primary mechanisms: racemization and oxidation. Racemization leads to d-epinephrine which is twenty times less active than l-epinephrine. There is less driving force for these decomposition reactions when the same quantity of epinephrine is dissolved in a smaller volume of solution. In other words, more concentrated epinephrine solutions are less prone to decomposition due to the kinetics of low volume solutions, relative to higher volume solutions. The stability of the epinephrine solutions is also enhanced by bubbling nitrogen through the solution to remove oxygen. However, it may not be possible to remove all of the oxygen by means of this technique. Utilizing a smaller volume solution results in less water and therefore less oxygen being present. Thus, the use of a smaller volume solution inherently reduces the amount of oxygen present. The use of volumes on the order of 10 to 20 milliliters or less for the acid solution are preferred.

The neutral, buffered solution and the acidic composition are sterilized and separately bottled or contained under sterile conditions by standard techniques, such as autoclaving, or use of sterilizing filters, but preferably by heat sterilization. Typically, the neutral, buffered solution, which primarily contains inorganic moieties, is autoclaved, whereas the acidic solution, which preferably contains the organic components, is microfiltered.

The above-described, two-part compositions may be packaged in various types of pharmaceutical containers. For example, the compositions may be packaged in a container having a first chamber for the neutral, buffered solution, an isolated second chamber for the acidic solution, and means to communicate the chambers without opening the container. The use of containers formed from Type I or Type-I SO_2 -treated glass are preferred.

The two-part compositions of the present invention may also be packaged by means of a combination of a bottle for the neutral, buffered solution and a syringe for the acidic composition containing one or more mydriatic agents. The acidic composition may be contained in the syringe as either a sterile solution or a sterile, lyophilized power. If it is in the form of a lyophilized powder, the powder may be reconstituted by drawing an amount

of the neutral, buffered solution sufficient to dissolve all of the powder into the syringe. A sterile diluent other than the neutral, buffered solution can also be utilized to dissolve the lyophilized powder. A two-compartment syringe can also be utilized, with the lyophilized powder in one compartment and a diluent for the powder in a second compartment. The compartments are separated by a movable stopper or membrane which can be displaced by depressing the plunger of the syringe, thereby allowing the diluent to be combined with the powder. Once the powder is dissolved, the resulting solution is then added to a bottle containing the neutral, buffered solution by inserting a cannula attached to the front of the syringe through a stopper in the top of the bottle.

The first and second parts can also be packaged in separate bottles. A sterile double-ended needle can be used to transfer the acidic solution to the neutral, buffered solution by aseptically inserting one end of the needle into a vial containing the acidic solution and then aseptically inserting the other end of the needle into the neutral, buffered solution package, whereby the vacuum that is maintained therein transfers the acidic solution to the neutral, buffered solution and is mixed.

The two-part composition of the present invention also provides an advantage as to safety if a technician should fail to properly mix the two solutions. The pH and osmolality of the larger volume neutral, buffered solution are at or near physiological levels, so that there is less chance of toxicity if the neutral, buffered solution were used without the acidic composition being mixed therewith.

The present invention may be embodied in various types of formulations. Representative formulations are described in the following examples.

EXAMPLE 1

The following two-part formulation is similar to the BSS Plus® brand intraocular irrigating solution available from Alcon Laboratories, Inc., Fort Worth, Texas, USA. That product, which is described in United States Patent No. 4,550,022 (Garabedian, et al.), consists of two solutions referred to as "Part I" and "Part II", respectively. The following description illustrates how that product or similar products could be modified to incorporate the present invention.

Part I (neutral, buffered solution) is made by dissolving sodium chloride, potassium chloride, and anhydrous dibasic sodium phosphate in water for injection at about 20° C. Then sodium bicarbonate is added and dissolved. Additional water for injection is added to make the desired volume and 1N HCl is added to adjust the pH to about 7.4. The solution is then passed through a 0.45 micron Millipore filter and placed in a bottle. The filled bottle is then stoppered, vacuumed and sealed. The sealed bottle is sterilized by autoclaving at 121° C for about 23 minutes.

Part II (acidic solution) is made by dissolving calcium chloride dihydrate, magnesium chloride hexahydrate, dextrose, reduced glutathione and epinephrine in water for injection. The solution is then sterile filtered through a 0.22 micron membrane filter and aseptically filled into a presterilized bottle and sealed with a presterilized rubber stopper.

When Parts I and II are combined, the composition of the resulting formulation is as follows:

	<u>Ingredients</u>	<u>Concentration (mM/l)</u>
15	Glutathione	0.01-3.0
	1 - Epinephrine	0.0005-0.11
	Bicarbonate	1-50
	Calcium	0.1-5
	Magnesium	0.1-10
20	Potassium	1-10
	Sodium	50-500
	Phosphate	0.1-5
	Glucose	1-25
	Chloride	50-500
25	Sodium Hydroxide	Adjust pH
	and/or	
	Hydrochloric Acid	Adjust pH
	Water for Injection	QS

As explained in greater detail in the following example, it is important to protect the Part II solution from light in order to prevent photo decomposition of the epinephrine.

EXAMPLE 2

The following formulation is a more specific example of the Part II solution described in Example 1 above:

	<u>Ingredients</u>	<u>Percent (weight/volume)</u>
5	Oxidized Glutathione, USP	0.46 + 25% xs
	1 - Epinephrine, USP	0.0025 + 10% xs
	Calcium Chloride (Dihydrate) USP	0.385
	Magnesium Chloride (Hexahydrate) USP	0.500
10	Dextrose Anhydrous, USP	2.3
	Sodium Hydroxide, NF and/or	QS to pH 2.0 to 6.0
	Hydrochloric Acid, NF	
	Water for injection, USP	QS to 100

15 This formulation may be prepared by means of the following procedure. First, all glassware is washed with hot water for injection ("WFI") depyrogenated at 250° before use. Then each of the following ingredients is sequentially added to about 80% of the total volume of WFI to be utilized, allowing each ingredient to dissolve before the next is added:

20 Calcium Chloride, Dihydrate, USP
Magnesium Chloride, Hexahydrate, USP
Dextrose, USP
Glutathione, USP
Epinephrine, USP

It should be noted that it is important to protect the solution from light, heat, metal surfaces
25 and oxygen after the addition of epinephrine. The pH of the solution is then checked and, if necessary, adjusted with hydrochloric acid NF and/or sodium hydroxide, NF. WFI is then added in an amount sufficient to reach 100% of the intended batch volume, and the resulting solution is mixed by stirring. The solution is then passed through a 0.2 micron membrane filter into a pyrogen-free container. The container is then flushed with nitrogen gas (a
30 nitrogen blanket is maintained over the solution to displace air and protect the solution from oxidation). Immediately after flushing the filled container with nitrogen gas, it is sealed by

means of a rubber stopper. The filled and sealed container is then placed in a cardboard box or sealed pouch to protect the contents, particularly epinephrine, from light during storage.

EXAMPLE 3

The following formulation represents another embodiment of the present invention, wherein phenylephrine is utilized as the mydriatic agent in the acidic solution instead of epinephrine.

<u>Ingredients</u>	<u>Percent (weight/volume)</u>
Calcium Chloride, dihydrate	0.385
Magnesium Chloride, hexahydrate	0.5
Dextrose, anhydrous	2.3
Glutathione Disulfide	0.46 + 10% xs
Phenylephrine Hydrochloride	0.005
Sodium Hydroxide, NF	Adjust pH
Hydrochloric Acid, NF	Adjust pH
Water for Injection	QS 100

This formulation can be prepared in accordance with the procedures described in Example 2 above.

The invention may also be embodied in products formulated or configured differently from the two-part product described above. For example, the acidic solution containing glutathione and epinephrine or another sympathomimetic compound can be lyophilized (i.e., freeze-dried) following preparation and then reconstituted as a solution prior to use. The low pH of the acid solution will have a stabilizing effect on epinephrine, both when the solution is initially formed, and after the lyophilized solution is reconstituted. The solution may be lyophilized in one basic step, or separate solutions may first be sequentially frozen in a single container, and then lyophilized, as described in United States Patent No. 4,975,419. The lyophilized powder must be stored in a sealed container, and that container should be placed in a sealed pouch constructed of a moisture impervious material, such as foil. The pouch should be opaque, in order to protect the epinephrine from light, and preferably also contains nitrogen gas, in order to protect the epinephrine from oxygen. If a bulking agent,

such as mannitol, is utilized to form the lyophilized powder, this may increase the osmolality of the solution, and therefore necessitate an adjustment in the amount of sodium chloride contained in the second part of the composition.

In view of the instability of epinephrine, special precautions may need to be taken during the manufacturing of the compositions of the present invention, particularly the first part which comprises epinephrine or another mydriatic agent. If epinephrine is utilized as the mydriatic agent, it will need to be protected from light, heat, oxygen and metal surfaces during the manufacturing process. In view of the sensitivity of epinephrine to light, only covered tanks or vessels should be used, and lighting of the area around the tanks or vessels should be reduced to the lowest extent possible. Ultraviolet light should be totally eliminated, if possible. The epinephrine should also be protected from oxygen during the manufacturing process. This protection may include the following steps:

- (1) using purified water, collected hot then cooled to 25-35°C with a nitrogen sparge, when compounding (or a closed, recirculating system w/N₂ head);
- (2) maintaining an N₂ purge of 3L/min from the bottom of the compounding reactor;
- (3) filtering all N₂ through a 0.22 um or smaller sterilizing filter;
- (4) prior to filling into final containers:
 - utilizing a portion of the solution to flush a glass-receiving reactor (carboy) and the filling apparatus, and
 - after filling the glass carboy, flushing a portion of the solution through fill needles to purge air from the lines;
- (5) filling into final containers shortly after compounding; and
- (6) providing continuous nitrogen flush to filled units prior to capping.

Other precautions which may need to be taken will be apparent to those skilled in the art.

What is Claimed is:

1. A sterile, preservative-free ophthalmic pharmaceutical composition for maintaining mydriasis and irrigating intraocular tissues during intraocular surgical procedures, said composition comprising a first part and a second part, said first part comprising an
5 acidic composition containing a mydriatic agent in an amount sufficient to maintain mydriasis, and said second part comprising a solution which comprises a buffer to provide an ophthalmically acceptable pH when said first part and said second part are combined .

2. A pharmaceutical composition according to Claim 1, wherein the pH of the first part is 3 to 5, and the pH of a solution resulting from the mixing of said first part and
10 said second part is 6.8 to 8.0.

3. A pharmaceutical composition according to Claim 2, wherein the mydriatic agent is a catecholamine.

4. A pharmaceutical composition according to Claim 3, wherein the catecholamine is selected from the group consisting of epinephrine, dipivalyl epinephrine, norepinephrine, phenylephrine and isoproterenol.
15

5. A pharmaceutical composition according to Claim 4, wherein the catecholamine comprises epinephrine.

6. A pharmaceutical composition according to Claim 2, wherein the composition comprises one or more electrolytes in an amount sufficient to facilitate the maintenance of
20 normal cellular function during an intraocular surgical procedure.

7. A pharmaceutical composition according to Claim 6, wherein the first part further comprises glutathione in an amount sufficient to facilitate the maintenance of normal cellular function during an intraocular surgical procedure.

8. A pharmaceutical composition according to Claim 7, wherein the glutathione consists essentially of oxidized glutathione.

9. A pharmaceutical composition according to Claim 8, wherein the concentration of the mydriatic agent in a solution formed by mixing the first part and the second part is
5 0.0005 to 0.11 mM/l.

10. A pharmaceutical composition according to Claim 9, wherein following mixing of the first part and the second part the composition comprises 0.1 to 5 mM/l calcium, 0.1 to 10 mM/l magnesium, 50 to 500 mM/l sodium, 1 to 10 mM/l potassium, 50 to 500 mM/l chloride, 0.1 to 5 mM/l phosphate, 1 to 50 mM/l bicarbonate, 1 to 25 mM/l dextrose and
10 0.01 to 3 mM/l oxidized glutathione.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/09912

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61K 37/00, 31/135

US CL : 514/19, 635, 912

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/19, 635, 912

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,550,022 (Garabedian et al) 19 October 1985. See the entire document.	1-10
Y	American Journal of Ophthalmology, Volume 110, issued July 1990, Slack et al, "A Bisulfite-Free Intraocular Epinephrine Solution," pages 77-82. See the entire document.	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T	Inter document published after the international filing date or priority date and not in conflict with the application but cited to understand the principles or theory underlying the invention
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P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

12 JANUARY 1994

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